I

S

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

Date: 6/22/11

MEMORANDUM

SUBJECT: **Hexythiazox.** Human Health Risk Assessment to Support Amended Use on Field Corn and New Use on Greenhouse Tomatoes.

PC Code: 128849	**DP Barcode:** 383744
Decision No.: 440296	**Registration No.:** 10163-277
Petition No.: 0E7787, 0F7773	**Regulatory Action:** Section 3 Registration
Risk Assessment Type: Single Chemical Aggregate	**Case No.:** N/A
TXR No.: NA	**CAS No.:** 78587-05-0
MRID No.: NA	**40 CFR:** 40 CFR 180.448

FROM: Donna S. Davis, Risk Assessor
Alexandra LaMay, Biologist
Linda Taylor, Toxicologist
Risk Assessment Branch VII
Health Effects Division (7509P)

THROUGH: Kit Farwell, DVM, Senior Toxicologist
Michael Metzger, Chief
Risk Assessment Branch VII
Health Effects Division (7509P)

TO: Olga Odiott, Risk Manger
Kimberly Nesci, PM Team 11
Insecticide Branch
Registration Division (7505P)

Attached please find the HED Human Health Risk Assessment for hexythiazox to support an amended use on field corn and a new use on greenhouse tomatoes.

Received in RRC 6/23/2011

Table of Contents

1.0 Executive Summary

Gowan Company is proposing amended registration of the 1 lb/gal emulsifiable concentrate (EC) formulation of hexythiazox (Onager ® Miticide, EPA Reg. No 10163-277) to reduce the preharvest intervals (PHIs) for field corn from 45 to 30 days and to expand the use from its current regionally restricted use to a national registration. In support of the proposed amendment, Gowan Company, under PP#0F7773, is proposing that the 40 CFR 180.448(a) be amended to reflect the following tolerances:

Corn, field, grain	0.02 ppm
Corn, field forage	6.0 ppm
Corn, field, stover	6.0 ppm
Aspirated grain fractions	0.50 ppm

In addition, IR-4 is proposing a new use of hexythiazox (Onager ® Miticide, EPA Reg. No 10163-277) on greenhouse tomatoes and under PP#0E7787 and has petitioned to establish a new tolerance under 40 CFR 180.448 (a) as follows:

Tomato	0.50 ppm

The toxicity database for hexythiazox is incomplete under the new 40 CFR Part 158 data requirements for conventional pesticides, which requires certain generic testing, including acute and subchronic neurotoxicity studies and an immunotoxicity study. However, the Agency believes that the current toxicity database is adequate to evaluate the hazards associated with these amended and new uses.

Hexythiazox has low acute toxicity by the oral, dermal and inhalation routes of exposure. It produces mild eye irritation, is not a dermal irritant, and is negative for dermal sensitization. The target organs of hexythiazox are the liver and adrenal glands in dogs, rats and mice, with the dog being the most sensitive species. Developmental toxicity was not observed in rabbits at the limit dose. Delayed ossification was observed in the rat at a dose level where decreased maternal body weight gain and food consumption were observed. In the reproductive toxicity study, decreased pup body weights were observed during lactation and delayed hair growth and/or eye opening were observed in the pups at the same dose levels where decreased parental body weight gain and increased absolute and relative liver, kidney, and adrenal weights were observed. Reproductive toxicity was not observed. The data provided no indication of increased susceptibility in rats or rabbits from *in utero* and postnatal exposure to hexythiazox. The toxicology database for hexythiazox does not show any evidence of treatment-related effects on the nervous system or the immune system. Hexythiazox is classified as "likely to be carcinogenic to humans"; however the evidence as a whole is not strong enough to warrant a quantitative estimation of human risk. Since the effects seen in the study that serves as the basis for the chronic RfD occurred at doses substantially below the lowest dose that induced tumors, the chronic RfD is considered protective of all chronic effects including potential carcinogenicity of hexythiazox.

No acute risk is expected since no hazard was identified in any toxicity study for this duration of exposure. Chronic risk is regulated based on effects seen in the adrenal glands in a one-year dog feeding study. Short-term and intermediate-term incidental oral and inhalation risks are regulated based on decreased pup body weight during lactation and delays in hair growth and/or eye opening, decreased parental body-weight gain and increased liver, kidney, and adrenal weights in the 2-generation reproduction study in the rat.

For the short- and intermediate-term dermal risk assessment, no quantification of risk is required, based on the fact that the oral equivalent dose for this dermal exposure scenario is 1.5-fold greater than the limit dose.

The overall weight of evidence suggests that this chemical does not directly target either the nervous system or the immune system. Although acute and subchronic neurotoxicity studies and an immunotoxicity study are required, the Agency does not believe that conducting these studies will result in lower PODs than those currently used for risk assessment, and therefore, a database uncertainty factor (UF_{DB}) is not needed to account for the lack of these studies. Further, since there is no evidence of reproductive or developmental toxicity, there is no increased sensitivity/susceptibility seen in the offspring, and exposure estimates are unlikely to underestimate risk; sufficient evidence exists to reduce the FQPA safety factor to 1X. All quantitative risk assessments employed inter- and intra- species uncertainty factors.

The nature and magnitude of the residue in plants, animals and water has been adequately delineated to support the proposed amended use on field corn and new use on greenhouse tomatoes. The submitted labels are adequate to support the proposed uses. An adequate high performance liquid chromatography method with UV detection (HPLC/UV) exists to enforce the recommended revised and new tolerances. Increased tolerances for ruminant meat byproducts to 0.05 ppm and for field corn stover at 7.0 ppm are required to support the amended and new uses. A decrease in the field corn forage tolerance to 3.0 is recommended. The current grain tolerance at 0.02 ppm is adequate to support the amended field corn use. A new tolerance on tomatoes at 0.5 ppm is required to support the proposed use on greenhouse tomatoes.

Codex MRLs are established for residues of hexythiazox on "edible offal (mammalian)" and "poultry, edible offal" at 0.05 ppm. A Codex MRL is established for tomatoes at 0.1 ppm. No other Codex, Canadian or Mexican MRLs are established for the commodities that are the subject of these petitions. Codex and U.S. tolerance expressions are harmonized at this time. Revision of the U.S. tolerances for meat byproducts to 0.05 ppm will result in harmonization with Codex for these commodities. Since the maximum residue seen in the U.S. green house tomato data is 0.34 ppm, harmonizing with the Codex MRL of 0.1 ppm at this time is not possible as over tolerance residues in the U.S. could result if the Codex MRL were adopted.

An acute endpoint was not selected for hexythiazox; therefore, the Agency conducted only a chronic dietary (food and drinking water) exposure and risk assessment. Chronic

dietary risks are not of concern for the U.S. population and all subpopulations.

Since there are no acute endpoints of concern, an acute aggregate risk assessment was not conducted. HED has conducted short-term, intermediate-term and long-term (chronic) aggregate risk assessments for hexythiazox. There are no aggregate risks of concern.

A quantitative dermal risk assessment is not required for hexythiazox. Occupational handler inhalation MOEs significantly exceed 100 for all scenarios assessed associated with the field corn and greenhouse tomato uses and are not of concern. Further, there were no risks of concern identified for postapplication exposure to hexythiazox associated with the field corn and tomato uses of this active ingredient.

No additional personal protective equipment (PPE) is required. The label restricted entry interval (REI) of 12 hours is appropriate and in compliance Worker Protection Standard requirements.

Potential areas of environmental justice concern, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

This assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide (i.e., from the Pesticide Handlers Exposure Database (PHED) and the Agricultural Reentry Task Force (ARTF)). A review of the ethical conduct of the applicable data has been completed and the studies met the criteria for being ethically conducted so their use in this Agency risk assessment is acceptable.

Regulatory Recommendation

Provided the registrant submits revised Section F (see Table 9.2) and further provided the toxicology studies detailed in Section 9.1 of this memorandum are required as a condition of registration, there are no human health risks of concern that would preclude the establishment/revision of tolerances for the residues of hexythiazox and its metabolites containing the (4-chlorophenyl)-4methyl-2-oxo-3-thiazolidine moiety under 40 CFR 180.448 (a) as follows:

Cattle, meat byproducts	0.05 ppm
Goat, meat byproducts	0.05 ppm
Hog, meat byproducts	0.05 ppm
Horse, meat byproducts	0.05 ppm
Sheep, meat byproducts	0.05 ppm
Corn, field, forage	3.0 ppm
Corn, field, stover	7.0 ppm
Grain, aspirated fractions	0.50 ppm
Tomato	0.50 ppm

***Note to RD**: Expired Section 18 tolerances for field corn commodities currently listed in the 40 CFR for hexythiazox can be removed in conjunction with the establishment of new/revised tolerances for field corn commodities.*

2.0 Ingredient Profile

Residue Chemistry Summary Document, D382910, D. Davis, 6/7/11

2.1 Summary of Registered/Proposed Uses

Gowan Company has submitted draft label language to support the amended use of hexythiazox on field corn. The amended label would reduce the PHI for field corn from 45 days to 30 days, expand the use to all areas of the country, and remove the prohibition limiting application after the V15 growth stage. No change to the application rate, number of applications or application technique is proposed.

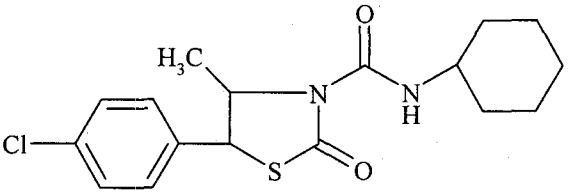
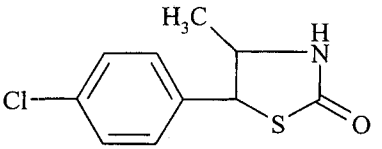
Additionally, IR-4 has submitted a proposed label for the new use on greenhouse tomatoes to permit foliar applications of hexythiazox to tomatoes with a 1-day PHI as a single application at a rate of up to 0.1875 lb ai/A.

The amended use directions for field corn and the newly proposed use directions for greenhouse tomatoes are presented in Table 2.1.

Table 2.1.	**Summary of Directions for Use of Hexythiazox.**					
Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Field Corn						
Foliar, Broadcast, Ground or Aerial	Onager 1 lb/gal EC [10163-277]	0.0469-0.1875	1	0.1875	30	Apply prior to adult mite build-up. Minimum spay volume for ground application of 15 – 20 gallons per acre (GPA). Minimum spray volume for aerial application of 5 GPA. Do not graze or feed livestock on cover crops growing in treated areas. Do not plant rotational crops other than those on this label within 120 days of application. Onager is an emulsifiable concentrate to be diluted with water for application in commercial plantings only.
Greenhouse Tomatoes						
Foliar	Onager 1 lb/gal EC [10163-277]	0.094 - 0.1875	1	0.1875	1	Apply prior to adult mite build-up. Minimum spray volume is 20 GPA. Onager is an emulsifiable concentrate to be diluted with water for application in commercial plantings only.

Conclusions. The label directions for field corn and greenhouse tomatoes are adequate to allow evaluation of the residue data relative to those proposed revised uses. The labels for use of Onager Miticide on field corn and greenhouse tomatoes are acceptable and are supported by the submitted data.

2.1.1 Structure and Nomenclature

Table 2.2 Structure and Nomenclature of Hexythiazox.	
Compound	
Common name	Hexythiazox
Company experimental names	DPX-Y5893, NA-73
IUPAC name	(4*RS*,5*RS*)-5-(4-chlorophenyl)-*N*-cyclohexyl-4-methyl-2-oxo-1,3-thiazolidine-3-carboxamide
CAS name	*trans*-5-(4-chlorophenyl)-*N*-cyclohexyl-4-methyl-2-oxo-3-thiazolidinecarboxamide
CAS #	78587-05-0
End-use product/EP	1 lb/gal EC (EPA Reg. No. 10163-277; Onager® 1E Ovicide/Miticide)
(4-chlorophenyl)-4-methyl-2-oxo-3-thiazolidine moiety	
Common name	PT-1-3 moiety
Chemical name	5-(4-chlorophenyl)-4-methyl-thiazolidin-2-one

2.3 Physical and Chemical Properties

Table 2.3. Physicochemical Properties of Hexythiazox.		
Parameter	Value	Reference[1]
Melting point/range	108.0-108.5 °C	00143533
pH	Not applicable	
Density	1.289 at 25 °C	00143533
Water solubility	0.12 ppm	44006301
Solvent solubility	g/L chloroform 1379 xylene 362 acetone 160.0 acetonitrile 28.6 n-hexane 3.9 methanol	00143533
Vapor pressure	$<10^{-8}$ mm Hg at 25 °C	44006301
Dissociation constant, pK_a	Not applicable	
Octanol/water partition coefficient Log(P_{OW})	560 (average)	0143533, 00146531
UV/visible absorption spectrum (molecular absorption coefficients)	Maximum at 223 nm in acetonitrile, no absorption in the visible range.	Not available

[1] References and values as cited in the petition materials for PP#9F7556.

3.0 Hazard Characterization/Assessment

3.1 Hazard Characterization

The toxicity database for hexythiazox is incomplete under the new 40 CFR Part 158 data requirements for conventional pesticides, which requires certain generic testing, including acute and subchronic neurotoxicity studies and an immunotoxicity study. However, Gowan Co. has committed to submit these data by December 2011 (letter from K. Smith, Registration Specialist, Gowan Co. to M. Suarez, PM 22, US EPA dated October 19, 2010). At this time, the Agency believes that the current toxicity database is adequate to evaluate the hazards associated with this new use.

Hexythiazox has a low order of acute toxicity and is classified as Toxicity Category IV for the oral, dermal and inhalation routes of exposure. It produces mild eye irritation (reddened conjunctiva) (Toxicity Category III), is not a dermal irritant (Toxicity Category IV), and is negative for dermal sensitization.

The target organs of hexythiazox (following both subchronic and chronic exposure) are the liver and adrenal glands in dogs, rats and mice, with the dog being the most sensitive species. In a subchronic toxicity study in rats, increased liver and adrenal weights, as well as adrenal histopathology (fatty degeneration of the adrenal zona fasciculata), were seen. In the chronic feeding/carcinogenicity studies in rats and mice, effects included decreased body weight gain and increased liver weights. In a 4-week range-finding study in dogs, effects included increased liver and adrenal weights. In the chronic dog study, increased liver and adrenal weights were observed, along with associated histopathology of the liver (hypertrophy) and adrenal glands (adrenal cortex hypertrophy).

Developmental toxicity was not observed in rabbits at the limit dose. Delayed ossification was observed in the rat at a dose level where decreased maternal body weight gain and food consumption were observed. In the reproductive toxicity study, decreased pup body weights were observed during lactation and delayed hair growth and/or eye opening were observed in the pups at the same dose levels where decreased parental body weight gain and increased absolute and relative liver, kidney, and adrenal weights were observed. Reproductive toxicity was not observed. The data provided no indication of increased susceptibility in rats or rabbits from *in utero* and postnatal exposure to hexythiazox. The toxicology database for hexythiazox does not show any evidence of treatment-related effects on the nervous system or the immune system.

EPA has classified hexythiazox as "likely to be carcinogenic to humans" based upon increased incidences of malignant and combined benign/malignant liver tumors in high-dose female B6C3F1 mice, and benign mammary gland tumors, observed in high dose male rats. There was no evidence of carcinogenicity in male mice and female rats. EPA concluded that the evidence as a whole was not strong enough to warrant quantitative estimation of carcinogenic risk to humans using a cancer slope factor based on the following considerations: (1) the liver tumors in B6C3F1 mice are a very common tumor in that species and were only observed in high dose females; (2) the mammary tumors in

rats were benign and were only observed in high dose male rats; and, (3) hexythiazox was shown to be non-mutagenic in mammalian somatic cells and germ cells. Additionally, the chronic NOAEL used for establishing the chronic RfD (2.5 mg/kg/day, from the one year toxicity feeding study in the dog), is approximately 65-fold lower than the lowest dose that induced tumors (in female mice at 163 mg/kg/day). Therefore, the chronic RfD of 0.025 mg/kg/day is judged to be protective of all chronic effects including potential carcinogenicity of hexythiazox.

3.2 Hazard Profile

The hazard profiles for hexythiazox are contained in Appendix A of this memorandum.

3.3 Dose-Response Assessment/Endpoint Selection

No endpoint attributable to a single exposure was identified from the available oral toxicity database; therefore, an acute dietary risk assessment for hexythiazox is not required.

The chronic dietary endpoint was selected from a one-year toxicity feeding study in the dog with a NOAEL of 2.5 mg/kg/day. At the study LOAEL of 12.5 mg/kg/day, increased absolute and relative adrenal weights and associated adrenal histopathology were observed. A 100X uncertainty factor was applied to account for inter- and intra-species variability resulting in a chronic reference dose (cRfD) of 0.025 mg/kg/day. Since the FQPA factor is reduced to 1X, the RfD is equivalent to the chronic population adjusted dose (cPAD).

Short-term and intermediate-term incidental oral and inhalation endpoints for risk assessment were selected from a two-generation reproduction study conducted in the rat with a NOAEL of 30 mg/kg/day. At the study LOAEL of 180 mg/kg/day, decreased pup body weight during lactation and delayed hair growth and/or eye opening, and decreased parental body-weight gain and increased absolute and relative liver, kidney, and adrenal weights were observed. In a subchronic toxicity study in rats, increased liver and adrenal weights, as well as adrenal histopathology (fatty degeneration of the adrenal zona fasciculata), were observed. Inhalation hazard is assumed to be equivalent to oral hazard.

For the short-term and intermediate-term dermal risk assessments, no quantification of risk is required, based on the fact that the dermal equivalent dose for this dermal exposure scenario is 1.5-fold greater than the limit dose considering the NOAEL of 30 mg/kg/day from the oral reproduction study, and the estimated 2% dermal absorption for this compound.

EPA has classified hexythiazox as "likely to be carcinogenic to humans" based upon increased incidences of malignant and combined benign/malignant liver tumors in high-dose female B6C3F1 mice, and benign mammary gland tumors, observed in high dose male rats. There was no evidence of carcinogenicity in male mice and female rats. EPA

concluded that the evidence as a whole was not strong enough to warrant quantitative estimation of carcinogenic risk to humans using a cancer slope factor.

3.4 FQPA Considerations

The Agency has determined that it is appropriate to reduce the FQPA safety factor to 1X for the following reasons:

- The toxicity database for hexythiazox is incomplete under the new 40 CFR Part 158 data requirements for conventional pesticides, which requires certain generic testing, including acute and subchronic neurotoxicity studies and an immunotoxicity study. However, the toxicology database does not show any evidence of treatment-related effects on the nervous system or the immune system. The overall weight of evidence suggests that this chemical does not directly target either system. Although acute and subchronic neurotoxicity studies and an immunotoxicity study are required as a part of new data requirements in the 40 CFR Part 158 for conventional pesticide registrations, the Agency does not believe that conducting these studies will result in a lower POD than any currently used for risk assessment, and therefore, a database uncertainty factor (UF_{DB}) is not needed to account for the lack of these studies.
- There is no evidence of increased susceptibility or sensitivity in rats or rabbits to pre- and/or post-natal exposure to hexythiazox.
- There is no evidence of neurotoxicity in the database. A developmental neurotoxicity (DNT) study is not required.
- The dietary risk assessment is highly conservative and not expected to underestimate risk.

3.5 Summary of Toxicological Doses and Endpoints for Use in Human Risk Assessments and Levels

Table 3.5.1 Toxicological Doses and Endpoints for Hexythiazox for Use in Dietary and Non-Occupational Human Health Risk Assessments [1]

Exposure/ Scenario	Point of Departure	Uncertainty /FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary All Populations	No risk is expected from this exposure scenario as no hazard was identified in any toxicity study for this duration of exposure			
Chronic Dietary *All Populations*	NOAEL=2.5 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF= 1x	Chronic RfD = 0.025 mg/kg/day cPAD = 0.025 mg/kg/day	One-Year Toxicity Feeding Study - Dog LOAEL = 12.5 mg/kg/day based on increased absolute and relative adrenal weights and associated adrenal histopathology.
Short- and Intermediate-Term Incidental oral	NOAEL=30 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF= 1x	Residential LOC for MOE = 100	2-Generation Reproduction Study – Rat LOAEL = 180 mg/kg/day, based on decreased pup body weight during lactation and delayed hair growth and/or eye opening, and decreased parental body-weight gain and increased absolute and relative liver, kidney, and adrenal weights 13-Week Oral Toxicity Study – Rat NOAEL = 5.5 mg/kg/day LOAEL = 38 mg/kg/day, based on increased absolute and relative liver weights in both sexes, increased relative ovarian and kidney weights, and fatty degeneration of the adrenal zona fasciculata. @ 397.5/257.6 mg/kg/day, decreased body-weight gain in females, slight swelling of hepatocytes in central zone (both sexes), increased incidence of glomerulonephrosis in males, increased adrenal weights
Cancer (oral, dermal, inhalation)	Classification: "Likely to be Carcinogenic to Humans". Insufficient evidence to warrant a quantitative estimation of human risk using a cancer slope factor based on the common liver tumors (benign and malignant) observed only in high dose female mice, and benign mammary gland tumors of no biological significance, observed only in high dose male rats in the absence of mutagenic concerns. The chronic RfD is protective of all chronic effects including potential carcinogenicity of hexythiazox.			

[1] Point of Departure (PoD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (intraspecies). UF_H = potential variation in sensitivity among members of the human population (interspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 3.5.2 Summary of Toxicological Doses and Endpoints for Hexythiazox for Use in Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short- and intermediate-Term	N/A	N/A	N/A	No dermal hazard identified
Inhalation Short- and Intermediate-Term	Oral NOAEL = 30 mg/kg/day Inhalation hazard assumed to be equivalent to oral hazard	UF_A=10x UF_H=10x	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	2-Generation Reproduction Study – Rat LOAEL = 180 mg/kg/day, based on decreased pup body weight during lactation and delayed hair growth and/or eye opening, and decreased parental body-weight gain and increased absolute and relative liver, kidney, and adrenal weights Co-critical 13-Week Feeding Study – Rat LOAEL = 38.1 mg/kg/day, based on increased absolute and relative liver weights in both sexes, increased relative ovarian and kidney weights, and fatty degeneration of the adrenal zona fasciculate.
Cancer (oral, dermal, inhalation)	Classification: "Likely to be Carcinogenic to Humans". ". Insufficient evidence to warrant a quantitative estimation of human risk using a cancer slope factor based on the common liver tumors (benign and malignant) observed only in high dose female mice, and benign mammary gland tumors of no biological significance, observed only in high dose male rats in the absence of mutagenic concerns. The chronic RfD is protective of all chronic effects including potential carcinogenicity of hexythiazox.			

[1] Point of Departure (PoD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (intraspecies). UF_H = potential variation in sensitivity among members of the human population (interspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

3.6 Endocrine disruption

As required under FFDCA section 408(p), EPA has developed the Endocrine Disruptor Screening Program (EDSP) to determine whether certain substances (including pesticide

active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Hexythiazox is on the EDSP List 2 which contains approximately 134 chemicals, many of them pesticides. This list was published in the Federal Register on 11/17/2010 (Volume 75, Issue 221), and is out for comment before being finalized, and before publication of the Schedule for Issuance of Test Orders.

For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

4.0 Dietary Exposure/Risk Characterization

4.1 Food Residue Profile

Residue Chemistry Summary Document, D382910, D. Davis, 6/7/11

The nature of the residue in plants, animals, and water has been adequately delineated. The residue of concern for the tolerance expression and risk assessment is for residues of the parent compound and its metabolites which contain the (4-chlorophenyl)-4-methyl-2-oxo-3-thiazolidine moiety. Residues of hexythiazox from foliar application tend to remain surface residues.

The submitted labels are adequate to support the proposed uses. An adequate high performance liquid chromatography method with UV detection (HPLC/UV) exists to enforce the recommended revised and new tolerances.

The amended use on field corn is supported by adequate, geographically representative residue data. The new use on greenhouse tomato is supported by an adequate number and variety (small-fruited vs. large-fruited) of residue data. The data support a reduction in the field corn forage tolerance to 3.0 ppm, and an increase in the field corn stover tolerance to 7.0 ppm. The current field corn grain tolerance of 0.02 ppm is adequate to support the amended use. The tomato greenhouse residue data support a new tolerance for tomatoes at 0.5 ppm. Updated maximum reasonably balanced diets (MRBD) for ruminants have been calculated and an increase in the meat byproduct tolerance is required. An adequate processing study to support the field corn use has been submitted. A tolerance of 0.5 ppm for aspirated grain fractions is required; no other

processing commodity tolerances are required to support the amended use on field corn. Since the tomato use is limited to greenhouse grown tomatoes which are intended for fresh market, processing data and processed commodity tolerances are not required. Codex MRLs are established for residues of hexythiazox on "edible offal (mammalian)" and "poultry, edible offal" at 0.05 ppm. A Codex MRL is established for tomatoes at 0.1 ppm. No other Codex, Canadian or Mexican MRLs are established for the commodities that are the subject of these petitions. Codex and U.S. tolerance expressions are harmonized at this time. Revision of the U.S. tolerances for meat byproducts to 0.05 ppm will result in harmonization with Codex for these commodities. Since the maximum residue seen in the U.S. green house tomato data is 0.34 ppm, harmonizing with the Codex MRL of 0.1 ppm at this time is not possible as over tolerance residues in the U.S. could result if the Codex MRL were adopted.

4.2 Drinking Water Residue Profile

EFED Field and Sweet Corn Drinking Water Assessment, D382948, D383019, A. Shelby, 1/3/10
EFED Greenhouse Tomato Drinking Water Assessment, D383745, A. Shelby, 12/1/10

The drinking water residues used in the dietary risk assessment were provided by the Environmental Fate and Effects Division (EFED) in the following memorandum: "Hexythiazox: Drinking Water Assessment for New Use on Field Corn, Sweet Corn, Dry Beans and Succulent Beans" (A. Shelby, D382948, D383019, 11/3/10) and incorporated directly into this dietary assessment. EFED evaluated the new use on greenhouse tomatoes (A. Shelby, D383745, 12/1/10) and concluded that water residues from the 11/3/10 uses would be higher and should represent this new use as well.

The Agency does not have monitoring data available to perform a quantitative drinking water risk assessment for hexythiazox. Therefore, the potential for hexythiazox residues in drinking water was evaluated through modeling.

Since previous assessments have indicated that surface water residue values greatly exceed groundwater estimated drinking water concentrations, EFED's updated drinking water assessment addressed surface water residues only, and surface water residues were used in HED's dietary risk assessment.

Surface water concentrations were estimated using the Tier II model Pesticide Root Zone Model 3 (PRZM3; ver. 3.12.2; 5/2/2005)/Exposure Analysis Modeling System (EXAMS; ver. 2.98.04.06; 4/25/2005). The model and its description are available at the EPA internet site: http://www.epa.gov/oppefed1/models/water/.

Since no environmental fate data has been submitted for the degradates of concern, EFED conducted a total residue exposure assessment. Because hexythiazox is used nationally on a variety of crops, the national default percent crop area (PCA) of 0.87 was applied. EFED evaluated scenarios intended to most closely match the existing and newly proposed uses, including application to corn in IL, MS, NC, OH and PA, as well as application of hexythiazox to beans in IL and soybeans in MS. Based on modeling results and the PCA adjustment, the maximum estimated surface water exposure

concentrations for total residues of hexythiazox for all currently proposed and established uses were from the MS soybean scenario and were:

6.6 µg/L for the 1 in 10 year annual peak concentration
4.5 µg/L for the 1 in 10 year annual average concentration
5.8 µg/L for the 21-day average concentration, and
5.2 µg/L for the 60-day average concentration

For the chronic dietary risk assessment, the 1 in 10 year annual average surface water concentration of 4.5 µg/L was used.

4.3 Dietary Exposure and Risk

Dietary Exposure and Risk Memorandum, D388134, D. Davis, 6/22/11

4.3.1 Acute Dietary Exposure/Risk

No toxic effects attributable to a single dose of hexythiazox were observed in the toxicology database; therefore, an acute dietary exposure and risk assessment for this chemical was not conducted.

4.3.2 Chronic Dietary Exposure/Risk

The chronic dietary risk assessment used tolerance level residues, included modeled drinking water estimates, assumed 100% crop treated, and incorporated DEEM default processing factors. This highly conservative risk assessment showed no risks of concern (<100% of the chronic population adjusted dose (cPAD)) for the U.S. General Population or any subpopulation. The estimated exposure to the U.S. General Population resulted in a risk equivalent to 12% of the cPAD. The estimated exposure to children 1 – 2 years of age, the most highly exposed subpopulation, resulted in a risk equivalent to 51% of the cPAD. Results for all subpopulations are summarized in Table 4.3.3, below.

4.3.3 Cancer Dietary Risk

The HED Cancer Assessment Review Committee (CARC) has recently reconsidered hexythiazox and has classified the chemical as "Likely to be Carcinogenic to Humans", but has determined that there is insufficient evidence to quantify risk using a cancer slope factor. Rather, the committee concluded that regulation based on the chronic reference dose will be protective for both chronic and carcinogenic risks. As noted above there are no chronic risks of concern.

Table 4.3.3. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Hexythiazox

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD*	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	N/A	N/A	0.003030	12	No concern for risks associated with the carcinogenic potential of hexythiazox.	
All Infants (< 1 year old)			0.005863	24	N/A	N/A
Children 1-2 years old			**0.012761**	**51**		
Children 3-5 years old			0.008814	35		
Children 6-12 years old			0.004476	18		
Youth 13-19 years old			0.002321	9.3		
Adults 20-49 years old			0.001951	7.8		
Adults 50+ years old			0.002191	8.8		
Females 13-49 years old			0.002086	8.3		

* Most highly exposed subpopulation is highlighted in bold.

4.4 Anticipated Residue and Percent Crop Treated (%CT) Information

Anticipated residues and percent crop treated information were not used in the dietary exposure and risk assessment conducted to support the amended and new uses of hexythiazox on field corn and greenhouse tomatoes.

5.0 Residential and Other Non-Occupational Exposures/Risks

D371715, A. LaMay, 3/23/10, Residential Exposure and Risk Assessment

There are no new residential uses proposed with the new use on greenhouse tomatoes and amended use on field corn. The residential handler and post-occupational exposures and risks were previously assessed in the memorandum cited above. Results of that assessment are summarized in the tables below.

5.1 Residential Handler Exposure and Risk

Table 5.1. Short-term Exposure and Risks for Residential Handlers

Exposure Scenario (Data Source)	Application Rate[1] (lb ai/ gallon)	Quantity Handled/ Treated per day[2]	Inhalation Unit Exposure (µg/ lb ai)[3]	Inhalation Dose (mg/kg/ day)[4]	Baseline Inhalation MOE [5]*
Mixer/Loader/ Applicator Scenarios					
Liquids/ Low Pressure Handwand (ORETF data OMA006)	0.0625 lb ai/ 100 gal	5 gallons	2.7	1.3E-7	220,000,000
Liquids/ Hose End Sprayer, Lawn (ORETF data OMA004)			17	7.6E-7	40,000,000
Hose End Sprayer (ORETF data OMA006)			0.82	3.7E-8	820,000,000
Hose End Sprayer on trees and ornamentals (ORETF data OMA005)			1.5	6.7E-8	450,000,000
Handheld pump spray on trees and ornamentals (ORETF data OMA005)			3.8	1.7E-7	180,000,000

[1]Application rates are based on maximum application rates of product.
[2]Quantity treated daily values are back-calculated from 5 gallons of finished spray solution being used per day (Revised Residential SOPs 2001) for outdoor products.
[3]Unit Exposure data sources are identified in the exposure scenario column. All exposure scenarios assess exposure reflecting applicators wearing short-sleeved shirts and shorts and no respiratory protection.
[4] Daily Inhalation Dose = (Inhalation Unit Exposure (µg ai / lb ai) * Conversion Factor (1 mg/ 1000 µg) * Application Rate (lb /gal) * Quantity handled (gallons/day)) / Body Weight (70 kg)
[5] Inhalation MOE = PoD (NOAEL of 30 mg/kg/day) / Daily inhalation dose (mg/kg/day)

5.2 Residential Postapplication Exposure

Table 5.2. Residential Post-application Short- and Intermediate-term Exposures and Risks for Hexythiazox

Exposure Scenario	Application Rate[1] (lb ai/A)	Exposed Population & Exposure Duration[2]	Daily Dose (mg/kg/day)[3]	MOE[4]
Treated Turf/ Lawn Exposure Scenarios				
Hand-to-Mouth from Treated Turf	0.19	Child ST	0.0028	11,000
		Child IT	0.0013	22,000
Object-to-Mouth from Treated Lawn		Child ST, IT	0.00071	42,000
Soil Ingestion in Lawn/ Garden		Child ST, IT	9.52E-6	3,200,000

[1] Application rates are based on maximum label application rate.
[2] ST= short-term duration; IT = intermediate-term duration.
[3] Daily Dose = Daily Dose algorithms for various residential post-application scenarios outlined in D371715.
[4] MOE = PoD (NOAEL of 30 mg/kg/day for short- and intermediate-term durations)/ Daily dose (mg/kg/day).

5.3 Other

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from groundboom application methods. The

Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT® computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

6.0 Aggregate Risk Assessments and Risk Characterization

6.1 Acute Aggregate Risk

No toxic effects attributable to a single dose of hexythiazox were observed in the toxicology database; therefore, an acute aggregate risk assessment for this chemical is not required.

6.2 Short- and Intermediate-Term Aggregate Risks

Short- and intermediate-term aggregate risks combine residential handler and post application exposures with average food and water exposures. Short- and intermediate-term aggregate margins of exposure for adults and children ranged from 1,900 to 15,000. Since the level of concern for these risk assessments is for MOEs less than 100, there are no short- or intermediate-term aggregate risks of concern. Table 6.2.1 summarizes the residential exposure values used in the short- and intermediate-term aggregate assessments and Table 6.2.2 summarizes the short- and intermediate-term aggregate risks.

Table 6.2.1. Short- and Intermediate-Term Residential Exposure Values and Sources Used in the Hexythiazox Aggregate Risk Assessment

Population	Handler Exposure (mg/kg/day)	Postapplication Exposure (mg/kg/day)	Residential Exposure (mg/kg/day)[1]
Short-Term			
Adult Male	7.6×10^{-7} Source: Table 5.1 Liquids/ Hose End Sprayer, Lawn	N/A	7.6×10^{-7}
Adult Female	7.6×10^{-7} Source: Table 5.1 Liquids/ Hose End Sprayer, Lawn	N/A	7.6×10^{-7}
Child	N/A	0.0028 Source: Table 5.2 Hand-to-Mouth from Treated Turf	0.0028
Intermediate-Term			
Adult Male	N/A	N/A	N/A
Adult Female	N/A	N/A	N/A
Child	N/A	0.0013 Source: Table 5.2 Hand-to-Mouth from Treated Turf	0.0013

[1] Residential exposure is the sum of the handler (adults only) and post application exposures.

[2] N/A is not applicable because there is no dermal endpoint.

Table 6.2.2. Short-Term and/or Intermediate-Term Aggregate Risk Calculations

Population	Short-Term Scenario					
	NOAEL mg/kg/day	LOC[1]	Max Allowable Exposure[2] mg/kg/day	Average Food & Water Exposure mg/kg/day	Residential Exposure[3] mg/kg/day	Aggregate MOE (food and residential)[4]
Adult Male	30	100	0.3	0.002191	7.6×10^{-7}	14,000
Adult Female	30	100	0.3	0.002191	7.6×10^{-7}	14,000
Child	30	100	0.3	0.012761	0.0028	1,900
	Intermediate-Term Scenario					
Adult Male	30	100	0.3	0.002191	N/A	14,000
Adult Female	30	100	0.3	0.002191	N/A	14,000
Child	30	100	0.3	0.012761	0.0013	2,100

[1] The LOC of 100 is based on the standard inter- and intra-species extrapolation factors.
[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC = 30/100 = 0.3 mg/kg/day.
[3] Residential Exposure values taken from Table 6.2.1.Average food & water exposure taken from Table 4.3.3.
[4] Aggregate MOE = [NOAEL)/ (Avg Food & Water Exposure + Residential Exposure)]

6.3 Long-Term (Chronic) Aggregate Risk

As there are no uses that are expected to result in long-term residential exposure, long-term aggregate risk includes average food and water residues only. As noted in Section 4.3.2 of this memorandum, there are no chronic dietary (food and water) risks of concern.

7.0 Cumulative Risk Characterization/Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to hexythiazox and any other substances and hexythiazox does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that hexythiazox has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

8.0 Occupational Exposures and Risks

D389550, A. LaMay, 5/10/11, Occupational Exposure and Risk Assessment

An occupation exposure and risk assessment was conducted to support the amended use on field corn and the new use on greenhouse tomatoes. Full details of that assessment are included in the memorandum cited above and the results are briefly summarized here.

8.1 Occupational Handler Risk

The occupational exposure and risk assessment addresses risks to workers exposed in an occupational setting via the dermal and inhalation routes of exposure. However, for hexythiazox a quantitative dermal risk assessment is not required; therefore risks were quantitatively assessed for inhalation exposure only. All occupational handler scenarios assessed for the amended field corn and new greenhouse tomato uses resulted in estimated inhalation margins of exposure (MOEs) which were significantly greater than 100 with baseline inhalation protection (no respirator). Therefore, inhalation risks are not of concern and inhalation personal protective equipment (PPE, i.e., respirators) is not required.

Occupational handler risks for field corn and greenhouse tomatoes are shown in Table 8.1.

Table 8.1. Short- and Intermediate-Term Inhalation Exposures and Risks for Occupational Handlers of Hexythiazox at Baseline Inhalation Protection (no respirator)

Exposure Scenario	Crop	Application Rate[1]	Inhalation Unit Exposure[2] (µg/lb ai)	Area/ Amount Treated Daily [3]	Inhalation Daily Dose (mg/kg/ day)[4]	Baseline Inhalation MOE[5]
Mixer/Loader Scenarios						
Mix/Load Liquids for Aerial Application	Field Corn	0.19 lb ai/A	0.219	1200 acres	0.000713	42,000
Mix/Load Liquids for Chemigation				350 acres	0.000208	140,000
Mix/Load Liquids for Groundboom Application				200 acres	0.000119	250,000
Mix/Load Liquid for High Pressure Handwand Application	Tomato	0.19 lb ai/20 gal		1000 gallons	0.0000297	1,000,000
Mixer/Loader/ Applicator Scenarios						
Mix/Load/Apply Liquid Flowable by Handgun Spray	Tomato	0.19 lb ai/A	1.9	5 acres	0.0000258	1,200,000
Mix/ Load/ Apply Liquid by Low Pressure Handwand	Tomato	0.19 lb ai/20 gal	30	40 gallons	1.63×10^{-4}	180,000
Mix/ Load/ Apply Liquid by Backpack sprayer			30	40 gallons	1.63×10^{-4}	180,000
Applicator Scenarios						
Applying Sprays by Enclosed Fixed-Wing Aircraft[6]	Field Corn	0.19 lb ai/A	Eng. Control: 0.068	1200 acres	0.00022	140,000
Applying Sprays by Open Cab Groundboom			0.34	200 acres	0.000185	160,000
High Pressure Handwand	Tomato	0.19 lb ai/20 gal	79	1000 gallons	0.01072	2,800
Flagger Scenario						
Flagging for Liquid Aerial Application	Field Corn	0.19 lb ai/A	0.35	1200 acres	0.0011	26,000

[1]Application rates are based on maximum values found on the label.
[2]Baseline inhalation unit exposures represent no respirator protection. All values are reported in the Occupational Pesticide Handler Unit Exposure Surrogate Reference Table dated May 2011, using PHED, AHETF, and ORETF data.
[3]Area treated daily values are from the EPA HED estimates of area treated in a single day for each exposure scenario of concern.
[4] Daily Inhalation Dose = (Inhalation Unit Exposure (µg ai / lb ai) * Conversion Factor (1 mg /1000 µg) * Application Rate (lb ai /A) * Area Treated (A/day or gal/day)) / Body Weight (70 kg).
[5] Inhalation MOE = PoD (NOAEL of 30 mg/kg/day for short- and intermediate-term exposure durations) / Daily inhalation dose (mg/kg/day).
[6] Application by fixed-wing aircraft has engineering control of enclosed cab.

8.2 Occupational Post Application Risk

HED uses the term postapplication to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Postapplication exposure levels vary over time and depend of such things as the type of activity, the nature of the crop or target that was

treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for postapplication exposure.

For the occupational dermal exposure pathway, short- and intermediate-term quantitative risks assessment were not conducted since quantification of dermal risk is not required for hexythiazox. Therefore no occupational dermal risks of concern have been identified for hexythiazox.

Based on the Agency's current practices, a quantitative occupational postapplication inhalation exposure assessment was not performed for hexythiazox at this time. However, there are multiple potential sources of postapplication inhalation exposure to individuals performing postapplication activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009. The Agency received the SAP's final report on March 2, 2010 (http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html). The Agency is in the process of evaluating the SAP report as well as available postapplication inhalation exposure data generated by the Agricultural Reentry Task Force and may, as appropriate, develop policies and procedures, to identify the need for and, subsequently, the way to incorporate occupational postapplication inhalation exposure into the Agency's risk assessments. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational postapplication inhalation exposure assessment for hexythiazox.

The label Restricted Entry Interval (REI) of 12 hours is appropriate and in compliance Worker Protection Standard requirements.

9.0 Data Needs and Label Recommendations

9.1 Toxicology

Based on revisions to the 40 CFR Part 158, additional toxicity data are required to support the continued registration of hexythiazox. The rule requires certain generic testing, including acute and subchronic neurotoxicity studies, and an immunotoxicity study which have not been submitted for this active ingredient. Since the toxicology database does not show any evidence of treatment-related effects on the nervous system or the immune system, these data requirements can be made a condition of registration.

9.2 Residue Chemistry

The following residue chemistry deficiencies have been identified.

860.1550 Proposed Tolerances

- The proposed tolerances must be revised as specified in Table 9.2.

Table 9.2. Tolerance Summary for Hexythiazox

Commodity	Tolerance (ppm)			Comments; *Correct Commodity Definition*
	Established	Proposed	Recommended	
40 CFR §180.448(a)				
Cattle meat byproducts	0.02	-	0.05	*Cattle, meat byproducts* An increase is required based on updated MRBD calculations and to harmonize with Codex MRL.
Goat meat byproducts	0.02	-	0.05	*Goat, meat byproducts* An increase is required based on updated MRBD calculations and to harmonize with Codex MRL.
Hog meat byproducts	0.02	-	0.05	*Hog, meat byproducts* An increase is required based on updated MRBD calculations and to harmonize with Codex MRL.
Horse meat byproducts	0.02	-	0.05	*Horse, meat byproducts* An increase is required based on updated MRBD calculations and to harmonize with Codex MRL.
Sheep meat byproducts	0.02	-	0.05	*Sheep, meat byproducts* An increase is required based on updated MRBD calculations and to harmonize with Codex MRL.
Field corn forage	6.0	-	3.0	*Corn, field, forage* Recommended tolerance based on outcome of OECD MRL calculator. Expired S18 tolerance under 180.448(b) can be removed from CFR.
Field corn grain	0.02	-	0.02	*Corn, field, grain* Expired S18 tolerance under 180.448(b) can be removed from CFR.
Field corn stover	-	6.0	7.0	*Corn, field, stover* Recommended tolerance based on outcome of OECD MRL calculator. Expired S18 tolerance under 180.448(b) can be removed from CFR.

Table 9.2. Tolerance Summary for Hexythiazox				
Commodity	Tolerance (ppm)			Comments; *Correct Commodity Definition*
	Established	Proposed	Recommended	
Aspirated grain fractions	-	0.50	0.50	*Grain, aspirated fractions* Correction to commodity definition required.
Greenhouse tomatoes	-	0.50	0.50	*Tomato*

9.3 Occupational/Residential Exposure

There are no data gaps with respect to occupational/residential exposure and risk assessment required to support the requested new use.

10.0 Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

11.0 Human Studies

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their dermal and inhalation exposure. Many such studies, involving exposure to many different pesticides, comprise generic pesticide exposure data sources such as the Pesticide Handlers Exposure

Database (PHED), the Agricultural Reentry Task Force (ARTF) Database, the Outdoor Residential Exposure Task Force (ORETF), and the Agricultural Handler Exposure Task Force (AHETF). EPA has reviewed all the studies in these multi-pesticide generic exposure data sources, and on the basis of available evidence has found them to have been neither fundamentally unethical nor significantly deficient relative to standards of ethical research conduct prevailing when they were conducted. There is no regulatory barrier to continued reliance on these studies, and all applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied.

Appendix A. Toxicity Profiles

Table A.1. Acute Toxicity Data on Hexythiazox Technical

Guideline No./ Study Type	MRID No.	Results	Toxicity Category
870.1100 Acute oral toxicity	00146549	LD_{50} = >5000 mg/kg	IV
870.1200 Acute dermal toxicity	00146550	LD_{50} = >5000 mg/kg	IV
870.1300 Acute inhalation toxicity	00146554	LC_{50} = >2.0 mg/L	IV
870.2400 Primary eye irritation	00146551	Reddened conjunctiva	III
870.2500 Acute dermal irritation	00146552	Non irritant	IV
870.2600 Skin sensitization	00146553	Non sensitizer	N/A

Table A.2. Toxicity Profile of Hexythiazox

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity (rat)	45067101 (1983) Acceptable/guideline 0, 10, 70, 500, or 3500 ppm M: 0, 1.2, 8.1, 58.6, or 397.5 mg/kg/day F: 0, 0.8, 5.4, 38.1 or 257.6 mg/kg/day	NOAEL = 8.1/5.4 mg/kg/day, males/females LOAEL = 58.6/38.1 mg/kg/day, males/females, based on increased absolute and relative liver weights in both sexes, increased relative ovarian and kidney weights, and fatty degeneration of the adrenal zona fasciculata. At the highest dose tested, 397.5/257.6 mg/kg/day, decreased body-weight gain in females, slight swelling of hepatocytes in central zone (both sexes), increased incidence of glomerulonephrosis in males, increased adrenal weights
870.3700a Prenatal developmental toxicity (rat)	44955711 (1984) Acceptable/guideline 0, 240, 720, or 2160 mg/kg/day	**Maternal** NOAEL = 240 mg/kg/day LOAEL = 720 mg/kg/day based on decreased maternal body weight gain, and decreased food consumption. **Developmental** NOAEL = 240 mg/kg/day LOAEL = 720 mg/kg/day based on delayed ossification.
870.3700b Prenatal developmental toxicity (rabbit)	00146555 (1984) Acceptable/guideline 0. 120, 360, or 1080 mg/kg/day	**Maternal** NOAEL ≥1080 mg/kg/day LOAEL >1080 mg/kg/day **Developmental** NOAEL ≥1080 mg/kg/day LOAEL >1080 mg/kg/day
870.3800 Two-Generation reproduction and fertility effects (rat)	00147578 (1985) Acceptable/guideline 0, 60, 400, or 2400 ppm Average doses across generations: M: 0, 4.45, 29.73, or 180.67 mg/kg/day F: 0, 5.27, 34.77, or 207.67 mg/kg/day	**Parental/Systemic** NOAEL = 29.73/34.77 mg/kg/day, males/females LOAEL = 180.67/207.67 mg/kg/day, males/females, based on decreased body weight gain and increased absolute and relative liver, kidney, and adrenal weights. **Reproductive** NOAEL ≥180.67/207.67 mg/kg/day, males/females LOAEL >180.67/207.67 mg/kg/day, males/females **Offspring** NOAEL = 29.73/34.77 mg/kg/day, males/females

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
		LOAEL = 180.67/207.67 mg/kg/day, males/females, based on decreased pup body weight during lactation, and delayed hair growth and/or eye opening.
870.4100b Chronic toxicity (dog)	00151359, 00146556, 00156895 (1984) Acceptable 0, 100, 500, or 5000 ppm (0, 2.5, 12.5, or 125 mg/kg/day) M: 0, 2.87, 13.1, or 153 mg/kg/day F: 0, 3.17, 13.9, or 148 mg/kg/day 4-week: 0, 125, 500, 2000, 8000 ppm	NOAEL = 2.5 mg/kg/day LOAEL = 12.5 mg/kg/day based on increased absolute and relative adrenal weights and associated adrenal histopathology (adrenal cortex hypertrophy). @ 125 mg/kg/day, relative adrenal weights and associated adrenal cortex hypertrophy (more pronounced) 4-week range-finding: relative adrenal weight increased at 2000 ppm (50 mg/kg/day) and 8000 ppm (200 mg/kg/day)
870.4300 Chronic Toxicity/ Carcinogenicity (rat)	00146559 (1984) Acceptable/guideline 0, 60, 430, or 3,000 ppm M: 0, 3, 23, or 163 mg/kg/day F: 0, 4, 29, or 207 mg/kg/day	NOAEL = 23/29 mg/kg/day, males/females LOAEL =163/207 mg/kg/day, males/females based on decreased body weight and body weight gain and increased absolute and relative liver weights in both sexes. **No evidence of carcinogenicity**
870.4300 Carcinogenicity (mouse)	00147577, 00156896 (1985) Acceptable/guideline 0, 40, 250, or 1500 ppm M: 0, 6.72, 41.6, or 267 mg/kg/day F: 0, 8.38, 51.2, or 318 mg/kg/day	NOAEL = 41.6/51.2 mg/kg/day, males/females LOAEL = 267/318 mg/kg/day, males/females) based on decreased male body weight and body weight gain, and increased absolute and relative liver weights in both sexes. **Evidence of carcinogenicity** (causes liver tumors in females).
Gene Mutation 870.5100 (*Salmonella typhimurium* and *Escherichia coli* reverse gene mutation assay)	44955710 (1983) Acceptable	The test was negative up to the highest dose tested (6400 µg/plate +/-S9.
Gene Mutation 870.5300 (*In vitro* mammalian cell forward gene mutation assay in CHO cells)	00155154 (1985) Acceptable	Independently performed trials were negative up to precipitating doses (≥60 µg/mL) and severely cytotoxic concentrations (200 µg/mL -S9; 400 µg/mL +S9).
Cytogenetics 870.5375 *In vitro* mammalian cell cytogenetic	00156894 (1986) Acceptable	The test was negative up to precipitating doses accompanied by severe cytotoxicity (≥167 µg/mL +/-S9).

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
assay in CHO cells		
Cytogenetics 870.5395 *In vivo* mouse micronucleus assay	44955708 Unacceptable	The results were inconclusive because a positive response, which was within the wide range of historical background data, was recorded for female mice at the mid-and high-doses (500 and 1000 mg/kg). The assay should be repeated to confirm or refute the equivocal results.
Other Effects 870.5550 *In vitro* UDS assay in primary rat hepatocytes	00156893 (1985) Acceptable	The test was negative up to a lethal dose (250 µg/mL).
870.7485 Metabolism and pharmacokinetics	00146558 (1985) Acceptable/guideline Single oral dose at 10 mg/kg (Group B); 14 daily oral doses (10 mg/kg) of unlabeled material followed by one dose (10 mg/kg) of [^{14}C] test material (Group C); and a single oral dose of 880 mg/kg (Group D).	Absorption and distribution of dosed radioactivity were rapid. The radioactive material was rapidly eliminated in the urine and feces; the majority of the radioactivity was eliminated within 24 hours. There were no observable differences in the total elimination of NA-73 between male and female rats. The major route of elimination in both the male and female rats was by fecal excretion. The major metabolite found, PT-1-8 (cis), accounted for 8-12% of the administered radioactivity in the low dose groups. Approximately 11-20% and 65-69% of the dosed radioactivity was identified as unchanged NA-73 in the low-dose and high-dose groups, respectively. All other metabolites were present at low concentrations (<2%). There was no apparent sex difference in metabolite formation. Significant levels of NA-73 equivalent [^{14}C]-residues were detected in the fat, liver, and adrenals. A sex-related difference in the residue levels of all tissues was observed, with residues in female tissues being two-fold higher than those found in male tissues.
870.7485 Metabolism and pharmacokinetics	0146557 (1983) Acceptable/non-guideline Single low dose (10 mg/kg/day)	Total recovery of radioactivity 72 hours after treatment accounted for 101.9-103% of the dose. The distribution of radioactivity 72 hours after dosing was as follows: 1) 30% (male and female) was excreted in the urine, 2) 60% (female) to 67% (male) was excreted in the feces, and 3) about 4% (male) to 10% (female) of the administered radioactivity remained in the tissues, with the highest concentration in the fat (2.3 ppm, males; 5.4 ppm, females). Significant sex differences existed for the pharmacokinetics of NA-73 in these rats, with females exhibiting slower elimination rats and higher tissue residues (about double) than males. NA-73 was metabolized to a large number of metabolites that were excreted both in the urine and feces. Seven metabolites were structurally identified in addition to the parent compound in both excreta of both sexes, with the major fecal metabolite, PT-1-8 (cis) accounting for 10% of the dosed radioactivity. The others were all minor metabolites accounting for less than 1.4%. About 20% of the dose was excreted as unchanged NA-73 (97% of which

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
		was in the feces). No significant sex difference was apparent with respect to metabolite formation.
870.7600 Dermal penetration	40608402, 40787901 (1985) Unacceptable	The total percent of dose absorbed averaged 2%, 1%, and 1.1% for cannulated rats (10-hour sacrifice) and 0.8%, 0.2%, and 0.2% for non-cannulated rats (1-hour sacrifice) at the low, medium, and high dose levels, respectively. The amount of radioactivity in the blood, carcass, urine and other organs totaled <2% of the applied dose. The results of this study (2% dermal absorption) can be used for risk assessment purposes.

13544

R192766

Chemical Name: Hexythiazox

PC Code: 128849
HED File Code: 14000 Risk Reviews
Memo Date: 6/22/2011
File ID: 00000000
Accession #: 000-00-0137

HED Records Reference Center
6/23/2011